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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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07/12/2001

Avi Ashkenazi

10466/70

4054

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7590

03/30/2005

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EXAMINER

KEMMERER, ELIZABETH

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

09/904,766

Applicant(s)

ASHKENAZI ET AL.

Examiner

Elizabeth C. Kemmerer, Ph.D.

Art Unit

1646

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 January 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 44-46 and 49-52.

Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: please see attachment.

12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____

13. ☐ Other: _____.

ATTACHMENT TO ADVISORY ACTION

Claims 44-46 and 49-52 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 44-46 and 49-52 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The basis of these rejections is of record.

Applicant's arguments (received 14 March 2005) have been fully considered but are not found to be persuasive for the following reasons. Only new arguments and evidence will be addressed. Applicant submits a declaration by Dr. Goddard under 37 CFR 1.132 as evidence that the method used in the specification has widespread recognition for versatility, sensitivity and accuracy.

The declaration by Dr Goddard under 37 CFR 1.132 filed 14 March 2005 is insufficient to overcome the rejection of claims 44-46 and 49-52 based upon 35 U.S.C. §§ 101 and 112, first paragraph as set forth in the last Office action for the following reasons. The declaration discusses the accuracy of the Taq DNA polymerase assay, stating that the Taqman PCR technique is sensitive enough to detect at least a 2-fold increase in gene copy number and that this increase is significant and useful. This is not deemed persuasive because it evinces that the instant specification provides a mere

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invitation to experiment, and not a readily available utility. The PRO269 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO269 nucleic acid was amplified in some cancers, to a minor degree (about 2 fold). No mutation or translocation of PRO269 has been associated with any type of cancer versus normal tissue. It is not known whether PRO269 is expressed in corresponding normal tissues, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO269 is amplified in a variety of samples, including some normal tissues, and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed “amplification” of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Furthermore, the Declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Goddard's conclusions are provided in the declaration. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a

5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicant also submits a declaration under 37 CFR 1.132 by Dr. Ashkenazi, with accompanying arguments. The declaration and arguments assert that, even when amplification of a gene in a tumor does not correlate with an increase in protein expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would also be useful; unfortunately, there is no evidence as to whether the gene products (such as the protein) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not present in currently available form, and is not substantial.

Applicant discusses the Orntoft, Hyman and Pollack references. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) *could only compare the levels of about 40 well-resolved and focused abundant proteins.*" (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between such low levels of amplification of DNA, found only in a minority of tested tumors which were not characterized on the basis of those in the Orntoft publication, and an associated rise in level of the encoded protein. Hyman (Cancer Research

62:6240-6245) found 44% of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO269 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression.

Applicant refers again to the Polakis declaration, and argues that the examiner's criticism of the declaration for failing to provide data is improper. However, given the evidence in the art that increased DNA amplification does not necessarily correlate with increased mRNA levels, and that increased mRNA levels do not necessarily correlate with increased protein levels, the examiner maintains that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO269 are specifically amplified in tumors. Further research would have to be done in order to determine if PRO 269 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to indicate PRO269 protein as a cancer marker.

Applicant criticizes the examiner's reliance on Hu et al. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal

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samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease.

However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Hanna et al. (Pathology Associates Medical Laboratories, 1999) show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Thus, the preponderance of the art supports the *prima facie* finding that a minor amplification of DNA would not form the basis for a substantial assertion of an association between PRO269 protein and cancer.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ECK

Elizabeth C. Hemmen

ELIZABETH C. HEMMEN
PATENT EXAMINER